The Claims

1. (Currently Amended) An apparatus comprising:

one or more processors; and

a memory coupled to the processors comprising one or more instructions, the processors operable when executing the instructions to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

determine a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

determine a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~generate a first set and at least a second set of empirically derived parameters, each set including a minimum binding-energy distance value and a well-depth value of the atom-pair type;~~

calculate a ~~first and second~~ repulsion term for ~~of~~ the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values ~~according to the first and second sets of empirically derived minimum binding-energy distance and well-depth values, respectively~~;

calculate a ~~first and second~~ potential of mean force (PMF) for ~~of~~ the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term ~~according to the calculated first and second repulsion terms, respectively, of the protein-ligand atom pair~~; and

calculate a ~~first and second~~ PMF score for ~~of~~ the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex ~~according to the calculated first and second PMF of the protein-ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex;~~

~~predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;~~

~~calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;~~

~~calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;~~

~~determine agreement between the first set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;~~

~~determine agreement between the second set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format~~.

2-8 (Canceled)

9. (Currently Amended) The apparatus of Claim 1, wherein one or more of the ~~first set of empirically derived~~ minimum binding-energy distance and well-depth values ~~or second sets of empirically derived minimum binding-energy distance and well-depth values~~ are each a product of one or more manual processes or automatic processes.

10. (Previously Presented) The apparatus of Claim 9, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

11. (Currently Amended) A method comprising:

determining, by one or more computer systems, an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

determining, by the one or more computer systems, a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

determining, by the one or more computer systems, a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~generating a first set and at least a second set of empirically derived parameters, each set including a minimum binding energy distance value and a well depth value of the atom pair type;~~

calculating, by the one or more computer systems, a ~~first and second~~ repulsion term for ~~of~~ the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values ~~according to the first and second sets of empirically derived minimum binding energy distance and well depth values, respectively~~;

calculating, by the one or more computer systems, a ~~first and second~~ potential of mean force (PMF) for ~~of~~ the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term ~~according to the calculated first and second repulsion terms, respectively of the protein ligand atom pair~~; and

calculating, by the one or more computer systems, a ~~first and second~~ PMF score for ~~of~~ the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex ~~according to the calculated first and second PMF of the protein ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein ligand complex;~~

~~predicting first and second structures of the protein ligand complex according to the first and second PMF scores, respectively;~~

~~calculating a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein ligand complex;~~

~~calculating a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein ligand complex;~~

~~determining agreement between the first set of empirically derived minimum binding energy distance and well depth values and the actual, analyzed protein ligand atom pair based at least in part on the first RMS deviation;~~

~~determining agreement between the second set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~communicating at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format~~.

12-18 (Canceled)

19. (Currently Amended) The method of Claim 11, wherein one or more of the ~~first set of empirically derived~~ minimum binding-energy distance and well-depth values ~~or second sets of empirically derived minimum binding-energy distance and well-depth values~~ are each a product of one or more manual processes or automatic processes.

20. (Previously Presented) The method of Claim 19, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

21. (Currently Amended) Software encoded in one or more computer-readable ~~tangible~~ storage media and when executed operable to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

determine a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

determine a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~generate a first set and at least a second set of empirically derived parameters, each set including a minimum binding energy distance value and a well depth value of the atom pair type;~~

calculate a ~~first and second~~ repulsion term for ~~of~~ the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values ~~according to the first and second sets of empirically derived minimum binding energy distance and well depth values, respectively~~;

calculate a ~~first and second~~ potential of mean force (PMF) for ~~of~~ the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term ~~according to the calculated first and second repulsion terms, respectively, of the protein ligand atom pair~~; and

calculate a ~~first and second~~ PMF score for ~~of~~ the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex ~~according to the calculated first and second PMF of the protein ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein ligand complex;~~

~~predict first and second structures of the protein ligand complex according to the first and second PMF scores, respectively;~~

~~calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein ligand complex;~~

~~calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein ligand complex;~~

~~determine agreement between the first set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;~~

~~determine agreement between the second set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user-readable format~~.

22-28 (Canceled)

29. (Currently Amended) The software of Claim 21 ~~Claim 25~~, wherein one or more of the ~~first set of empirically derived~~ minimum binding-energy distance and well-depth values ~~or second sets of empirically derived minimum binding-energy distance and well-depth values~~ are each a product of one or more manual processes or automatic processes.

30. (Previously Presented) The software of Claim 29, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

31. (Currently Amended) A system comprising:

means for determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

means for determining a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

means for determining a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~means for generating a first set and at least a second set of empirically derived parameters, each set including a minimum binding-energy distance value and a well-depth value of the atom-pair type;~~

means for calculating a ~~first and second~~ repulsion term for ~~of~~ the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values ~~according to the first and second sets of empirically derived minimum binding-energy distance and well-depth values, respectively~~;

means for calculating a ~~first and second~~ potential of mean force (PMF) for ~~of~~ the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term ~~according to the calculated first and second repulsion terms, respectively of the protein-ligand atom pair~~; and

means for calculating a ~~first and second~~ PMF score for ~~of~~ the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex ~~according to the calculated first and second PMF of the protein-ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex;~~

~~means for predicting first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;~~

~~means for calculating a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;~~

~~means for calculating a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;~~

~~means for determining agreement between the first set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;~~

~~means for determining agreement between the second set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~means for communicating at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format~~.

32. (New) The system of Claim 1, wherein the minimum binding-energy distance value is an empirically derived value.

33. (New) The system of Claim 1, wherein the well-depth value is an empirically derived value.

34. (New) The system of Claim 1, wherein:

the minimum binding-energy distance and well-depth values are part of a first set of minimum binding-energy distance and well-depth values;

the calculated repulsion term represents a first repulsion term;

the calculated PMF represents a first PMF;

the calculated PMF score represents a first PMF score; and

the processors are further operable when executing the instructions to:

determine a second set of minimum binding-energy distance and well-depth values, the second set comprising:

at least a second minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the second minimum binding-

energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

at least a second well-depth value for the protein-ligand atom pair based on the atom-pair type, the second well-depth value representing an amount of binding interaction for the atom-pair type;

calculate a second repulsion term for the protein-ligand atom pair based on the second minimum binding-energy distance and second well-depth values;

calculate a second potential of mean force (PMF) of the protein-ligand atom pair based on the second repulsion term; and

calculate a second PMF score for the protein-ligand complex based on the second PMF, the second PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex .

35. (New) The system of Claim 34, wherein the processors are further operable when executing the instructions to:

predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;

calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;

calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;

determine agreement between the first set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;

determine agreement between the second set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and

communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.

36. (New) The method of Claim 11, wherein the minimum binding-energy distance value is an empirically derived value.

37. (New) The method of Claim 11, wherein the well-depth value is an empirically derived value.

38. (New) The method of Claim 11, wherein:

the minimum binding-energy distance and well-depth values are part of a first set of minimum binding-energy distance and well-depth values;

the calculated repulsion term represents a first repulsion term;

the calculated PMF represents a first PMF;

the calculated PMF score represents a first PMF score; and

the method further comprises:

determining a second set of minimum binding-energy distance and well-depth values, the second set comprising:

at least a second minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the second minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

at least a second well-depth value for the protein-ligand atom pair based on the atom-pair type, the second well-depth value representing an amount of binding interaction for the atom-pair type;

calculating a second repulsion term for the protein-ligand atom pair based on the second minimum binding-energy distance and second well-depth values;

calculating a second potential of mean force (PMF) of the protein-ligand atom pair based on the second repulsion term; and

calculating a second PMF score for the protein-ligand complex based on the second PMF, the second PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex .

39. (New) The method of Claim 38, further comprising:

predicting first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;

calculating a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;

calculating a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;

determining agreement between the first set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;

determining agreement between the second set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and

communicating at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.

40. (New) The software of Claim 21, wherein the minimum binding-energy distance value is an empirically derived value.

41. (New) The software of Claim 21, wherein the well-depth value is an empirically derived value.

42. (New) The software of Claim 21, wherein:

the minimum binding-energy distance and well-depth values are part of a first set of minimum binding-energy distance and well-depth values;

the calculated repulsion term represents a first repulsion term;

the calculated PMF represents a first PMF;

the calculated PMF score represents a first PMF score; and

the software is further operable when executed to:

determine a second set of minimum binding-energy distance and well-depth values, the second set comprising:

at least a second minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the second minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

at least a second well-depth value for the protein-ligand atom pair based on the atom-pair type, the second well-depth value representing an amount of binding interaction for the atom-pair type;

calculate a second repulsion term for the protein-ligand atom pair based on the second minimum binding-energy distance and second well-depth values;

calculate a second potential of mean force (PMF) of the protein-ligand atom pair based on the second repulsion term; and

calculate a second PMF score for the protein-ligand complex based on the second PMF, the second PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex .

43. (New) The software of Claim 42, wherein the software is further operable when executed to:

predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;

calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;

calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;

determine agreement between the first set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;

determine agreement between the second set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and

communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.